

January 23, 2003

Timothy Adams, Ph.D.  
Technical Contact  
The Flavor and Fragrance High Production  
Volume Consortia  
Terpene Consortium  
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Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Aromatic Terpene Hydrocarbons posted on the ChemRTK HPV Challenge Program Web site on September 30, 2002. I commend The Flavor and Fragrance High Production Volume Consortia's Terpene Consortium for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The Flavor and Fragrance High Production Volume Consortia's Terpene Consortium advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at [tsca-hotline@epa.gov](mailto:tsca-hotline@epa.gov).

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director  
Risk Assessment Division

Enclosure

cc: C. Auer  
A. Abramson  
W. Penberthy  
M. E. Weber

## **EPA Comments on Chemical RTK HPV Challenge Submission: Aromatic Terpene Hydrocarbons**

### **SUMMARY OF EPA COMMENTS**

The sponsor, the Terpene Consortium of the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries to EPA for Aromatic Terpene Hydrocarbons dated June 26, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 30, 2002. The submission is for one chemical, *p*-cymene (*p*-methylisopropylbenzene, CAS No. 99-87-6).

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties and Environmental Fate. The physicochemical properties and environmental fate data provided by the submitter are adequate for the purposes of the HPV Challenge Program. However, there are some deficiencies in the robust summaries that the submitter needs to address. EPA agrees with the submitter that *p*-cymene be tested for biodegradability.
2. Health Effects. Adequate data are available for all health endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.
3. Ecological Effects. EPA agrees with the test plan for these endpoints.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

### **EPA Comments on the Aromatic Terpene Hydrocarbons Challenge Submission**

#### **Test Plan**

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program.

*Stability in water.* Even though it is indicated in the test plan (page 12) that this chemical does not hydrolyze in water, the submitter needs to provide this information in a robust summary, and explain why hydrolysis is not possible.

*Biodegradation.* EPA agrees with the submitter's proposal to test the biodegradability of *p*-cymene following OECD guidelines. To evaluate this endpoint, the submitter should follow OECD Guideline 301-Ready Biodegradability.

#### Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

EPA agrees with the submitter's test plan to use cumene as an analog to *p*-cymene, based on toxicokinetic data for both compounds, to provide supporting data for health endpoints. An additional reference on cumene metabolites in rabbits (Ishida and Matusmoto, 1992) would tend to enhance the case for using cumene as an analog; this reference mentions the omega-hydroxylation of cumene that is equivalent to the process discussed for *p*-cymene on page 9 of the test plan.

Adequate data are available for the acute toxicity of *p*-cymene and cumene, and for the repeated-dose, genetic, reproductive and developmental toxicity of cumene for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

#### Ecological Effects (fish, invertebrates, and algae).

The available data are adequate for fish and aquatic invertebrates. EPA agrees with the submitter's plan to conduct an algal inhibition study with *p*-cymene.

### **Specific Comments on the Robust Summaries**

#### Environmental Fate.

*Photodegradation.* The submitter needs to provide information on the concentration of hydroxyl radicals used to determine the reported half-life.

*Fugacity.* In the robust summary and test plan the submitter erroneously cited the fugacity model used as the "EQC Level III" model. In fact the submitter used the Level III model found in EPIWIN. The submitter also states that the model does not take biodegradation into account. This is incorrect. As a default, the Level III model derives biodegradation half-lives for soil, water and sediment from the results of the BOWIN biodegradation model. Furthermore, EPIWIN version 3.10 allows these default values to be changed by the user (the EQC Level III model can be found in the website of the Canadian Environmental Modeling Centre at Trent University at <http://www.trentu.ca/cemc/EQC.html>).

The submitter needs to incorporate in its robust summary the values of the input parameters.

#### Health Effects.

*Acute Toxicity.* Information missing from the acute oral study in rats exposed to *p*-cymene (MacDonald, 1961) includes the purity of the test material, the vehicle (if used), mortality results by sex, body weight changes, and statistical analysis.

*Repeated-Dose Toxicity.* The same reference (Cushman, et al 1995) is cited for two robust summaries for 13-week inhalation studies in rats on cumene with different protocols, different dose levels, different numbers of test animals and one with a 4-week recovery period, but same NOAEL and LOAEL. The submitter needs to clarify the discrepancies and specify which study is used for the reproductive toxicity endpoint. The submitter also needs to provide evaluation of the reproductive organs in the summaries.

*Genetic Toxicity.* The submitter needs to provide the purity of the test substance for both the *in vitro* Ames reverse mutation test (Lawlor and Wagner, 1987) and the *in vivo* micronucleus assay studies and the statistical analysis for the *in vitro* study.

*Reproductive Toxicity.* No studies were submitted. This endpoint is addressed by documentation of the evaluation of reproductive organs of male rats in a 13-week inhalation study on cumene and the availability of an adequate developmental toxicity study, but no data were submitted for females. The submitter needs to revise the robust summary to include histopathology results for female reproductive

organs in this study.

*Developmental Toxicity.* A robust summary for a developmental toxicity study in rats gestationally exposed by inhalation to cumene provided sufficient information to evaluate the study, but incorrectly identified the maternal LOAEL (stated to be lower than the NOAEL). The submitter needs to correct this error.

### **Followup Activity**

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

### **References**

Ishida, T. and T. Matsumoto. 1992. Enantioselective metabolism of cumene. *Xenobiotica*. 22(11): 1291-1298. [cited in NTP Nomination History and Review for Cumene CAS No. 98-82-8. online at [http://ntp-server.niehs.nih.gov/Chem\\_Background/ExecSumm/Cumene.html](http://ntp-server.niehs.nih.gov/Chem_Background/ExecSumm/Cumene.html)]